IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Masayuki Tsuchiya et al.	Art Unit :	1656
Serial No.	: 09/830,144	Examiner :	Sheridan L. Swope
Filed	: April 20, 2001	Confirmation No.:	9796
		Notice of Allowance Date: August 12, 2005	
Title	: METHOD FOR SCREENING COMPOUNDS INHIBITING SIGNAL TRANSDUCTION THROUGH INFLAMMATORY CYTOKINES		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed August 12, 2005, enclosed are a completed issue fee transmittal form PTOL-85B, Comments on Statement of Reasons for Allowance, and a check for $1430 for the required fee, including ten (10) patent copies.

Please apply any additional charges or credits to our Deposit Account No. 06-1050.

Respectfully submitted,

Date: Oct. 27, 2005

Reg. No. 44,164

FW Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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October 27, 2005
Date of Deposit

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COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

The Examiner's statement of reasons for allowance refers to the Notice of Allowance mailed December 27, 2004. Briefly, the Examiner alleged that it would have been obvious to test any compound that inhibits TAK1/TAB1 binding for inhibition of TGF-β-induced expression of IL-1, IL-6, IL-10 and TNF in view of the references previously cited (page 3 of the Notice of Allowance mailed December 27, 2004). The allowed claims, however, relate to a method of screening for compounds that inhibit the production of inflammatory cytokines that are produced in response to IL-1α or LPS. According to the Examiner, the ability of TAB1 and TAK1 to mediate LPS- or IL-1α-induced cytokine production was not known in the art prior to the filing date of the instant application, thus the instant invention is non-obvious over the prior art. *Id.*

While Applicants agree that the instant invention is non-obvious over the prior art, Applicants do not concede that it would have been obvious to test any compound that inhibits TAK1/TAB1 binding for inhibition of TGF-β-induced expression of IL-1, IL-6, IL-10 and TNF in view of the references previously cited. IL-1, IL-6, IL-10 and TNF are all pro-inflammatory cytokines. As discussed in the response submitted on October 7, 2004, the cited references teach:

- TAK1 binds to TAB1, and TAB1 may function as an activator of TAK1 in TGF-β signal transduction (Shibuya et al., Science 272(5265):1179-82, 1996);

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- TGF-β is a pleiotropic factor and acts on diverse tissue and cell types, not just the immune system. With respect to inflammation, TGF-β may be both pro-inflammatory and anti-inflammatory. The balance between these two opposing activities is crucial to maintaining immunological homeostasis in the host. There are multiple receptors and signal transduction mediators for TGF-β (McCartney-Francis et al., Int. Rev. Immunol. 16(5-6):553-80, 1998, and Letterio et al., Annu. Rev. Immunol. 16:137-61, 1998);
- TGF-β enhances the ability of macrophages to produce IL-10 (Maeda et al., J. Immunol. 155(10):4926-32, 1995); and
- methods of systemically analyzing the structure and function of peptides (Wells et al., U.S. Patent No. 5,580,723).

Thus, TGF-β has many different functions, including both pro-inflammatory and anti-inflammatory activities. There are multiple receptors and signal transduction mediators for these TGF-β functions. Absent specific teachings, a person of ordinary skill would not be able to recognize which mediator of TGF-β signal transduction is responsible for which of the diverse functions of TGF-β. The cited references teach only that TAK1-TAB1 may mediate TGF-β functions. Nothing in the cited references teaches the role of TAK1-TAB1 in TGF-β-induced inflammation, let alone TGF-β-induced expression of IL-1, IL-6, IL-10 and TNF. Therefore, there is no motivation or suggestion for a skilled artisan to combine the cited references and come to the conclusion that TAK1-TAB1 mediates the induction of IL-1, IL-6, IL-10 and TNF by TGF-β, rather than another TGF-β activity. The combined teaching also provides no reasonable expectation of success for the claimed invention, as, in view of the art, TAK1-TAB1 could have proven to be responsible for any of the numerous other TGF-β functions instead of inflammation.

Accordingly, it would <u>not</u> have been obvious to test any compound that inhibits TAK1/TAB1 binding for inhibition of TGF-β-induced expression of IL-1, IL-6, IL-10 and TNF.

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